TURKISH JOURNAL OF EMERGENCY MEDICINE

Original Article

Access this article online

Quick Response Code:

Website: www.turkjemergmed.com

DOI: 10.4103/2452-2473.367399

Sepsis-related pediatric acute respiratory distress syndrome: A multicenter prospective cohort study

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Abstract:

OBJECTIVES: This study aimed to compare the risk factors and outcomes for organ dysfunction between sepsis-related Pediatric acute respiratory distress syndrome (PARDS) and nonsepsis PARDS.

METHODS: We prospective cohort recruited intubated patients with PARDS at four tertiary care centers in Thailand. The baseline characteristics, mechanical ventilation, fluid balance, and clinical outcomes were collected. The primary outcome was organ dysfunction.

RESULTS: One hundred and thirty-two mechanically ventilated children with PARDS were included in the study. The median age was 29 months and 53.8% were male. The mortality rate was 22.7% and organ dysfunction was 45.4%. There were 26 (19.7%) and 106 (80.3%) patients who were classified into sepsis-related PARDS and nonsepsis PARDS, respectively. Sepsis-related PARDS patients had a significantly higher incidence of acute kidney injury (30.8% vs. 13.2%, $P = 0.041$), septic shock (88.5% vs. 32.1%, $P < 0.001$), organ dysfunction (84.6% vs. 35.8%, $P < 0.001$), and death (42.3% vs. 17.9%, $P = 0.016$) than nonsepsis PARDS group. Multivariate analysis adjusted for clinical variables showed that sepsis-related PARDS and percentage of fluid overload were significantly associated with organ dysfunction (odds ratio [OR] 11.414; 95% confidence interval [CI] 1.40892.557, $P = 0.023$ and OR 1.169; 95% CI 1.0121.352, $P = 0.034$).

CONCLUSIONS: Sepsis-related PARDS patients had more severe illness, organ dysfunction, and mortality than nonsepsis PARDS patients. The higher percentage of fluid overload and presentation of sepsis was the independent risk factor of organ dysfunction in PARDS patients.

Keywords:

Organ dysfunction, outcomes, pediatric, pediatric acute respiratory distress syndrome, risk factors, sepsis

Submitted: 18-08-2022
Revised: 14-10-2022
Accepted: 10-11-2022
Published: 09-01-2023

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Introduction

Pediatric acute respiratory distress syndrome (PARDS) is a clinical syndrome characterized by inhomogeneous noncardiogenic pulmonary edema caused by disruption of the alveolar epithelial-endothelial permeability barrier.[1] The prevalence of PARDS is approximately 6%10% among mechanically ventilated children.[2,3] The overall mortality rate decreases from 40%50% to 20%30%.[4] The PARDS risk factors are classified as direct

How to cite this article: Prasertsan P, Anantasit N, Walanchapruk S, Roekworachai K, Samransamruajkit R, Vaewpanich J. Sepsis-related pediatric acute respiratory distress syndrome: A multicenter prospective cohort study. Turk J Emerg Med 2023;23:96-103.

BOX-ED section

What is already known on the study topic?

- Pediatric acute respiratory distress syndrome (PARDS) is a life-threatening condition with a high mortality rate in critically ill children. The pathogenesis of PARDS varies depending on whether direct or indirect lung injury occurs. Sepsis is the most common cause of indirect lung injury, while pneumonia is the most common cause of direct lung injury.

What is the conflict on the issue? Has it importance for readers?

- There is inadequate evidence to compare the clinical risk factors and outcomes of PARDS patients with and without sepsis.

How is this study structured?

- This was a multicenter, prospective cohort study involving 132 patients with PARDS.

What does this study tell us?

- According to the finding of this study, the incidence of sepsis-related PARDS was 19.7%. PARDS patients with sepsis experienced more severe disease and higher organ dysfunction than those without sepsis. The percentage of fluid overload and sepsis-related PARDS were the independent risk factor of organ dysfunction in PARDS patients. Patients with higher PRISM III, PELOD scores, percentage of fluid overload, initial oxygen index, and lactate were associated with increased organ dysfunction in a subgroup analysis of the nonsepsis PARDS group. While only higher PRISM III was associated with increased organ dysfunction in the sepsis-related group.

lung injury and indirect lung injury. The most common risk factors for PARDS, according to a recent multicenter retrospective study, were pneumonia (79.5%), sepsis (11.4%), and near-drowning (4.6%), respectively.[5] The prior adult study indicated that the pathogenesis of acute respiratory distress syndrome (ARDS) differed between indirect and direct lung injury.[6] The indirect ARDS is characterized by increased vascular endothelial activation, while the direct ARDS is characterized by epithelial injury.[6,7] The prevalence of infections as the inciting etiology for PARDS ranges 40%82% in direct lung injury, and ranges from 19% to 26% in indirect lung injury etiology.[8,9] A recent retrospective study compared the outcomes of direct and indirect lung injury in children with ARDS. After adjusting for confounding variables, there was no difference in mortality outcomes between the two groups.[5] Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection.[10] The prevalence of PARDS in sepsis is unknown. Two studies found that the prevalence of ARDS in sepsis was significantly different (9% using the American European Consensus Conference definition and 83% using a loose definition of respiratory dysfunction).[11,12] A previous study showed adult patients with sepsis-related ARDS have a higher mortality, a lower successful extubation rate, and prolonged intensive care unit (ICU) stay than nonsepsis ARDS.[13] The clinical outcomes of PARDS in the presence of sepsis versus PARDS in the absence of sepsis have been poorly described. We hypothesized that PARDS in patients with sepsis would be more severe and have a higher mortality rate than PARDS in patients without sepsis. The purpose of this study was to compare the risk factors and outcomes of organ dysfunction in PARDS patients with sepsis risk factors (sepsis-related PARDS) and without sepsis risk factors (nonsepsis PARDS).

Methods

Study design and study population

This prospective cohort, multicenter study was conducted in the pediatric ICU (PICU) of four tertiary referral centers in Thailand. They serve as Thailand's regional referral centers for pediatric subspecialty care. They are capable of providing high-frequency oscillatory ventilation, nitric oxide, and extracorporeal life support. The screened patients were children 1 month to 18-year-old who required intubation during the study period from April 2017 to October 2018. Radiologists routinely evaluated chest radiographs of all PICU patients. All critically ill children who were admitted to PICU with PARDS were included either by the Pediatric Acute Lung Injury Consensus Conference (PALICC) or Berlin definitions.[14,15] The exclusion criteria were premature neonates with a corrected age <35 weeks, congestive heart failure, or perinatal-related lung disease. We obtained ethical approval from the Ethical Approval from institutional review board of the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Investigational Review Board and Ethic Committee of the Faculty of Medicine, Prince of Songkla University, Research and journal Management Committee Nakornping Hospital, Med Chula IRB with the approval code of COA. MURA2017/14, REC 60-077-19-1, EMID:0e1a497022346ec5, IRB 1642/2559. Written informed consents were obtained from the legal guardians of the children. The primary outcome was organ dysfunction. Secondary outcomes included mortality, length of ICU stay, and length of hospital stay.

Data collection

The demographic data were recorded, including age, gender, comorbidities, Pediatric Logistic Organ Dysfunction score (PELOD), Pediatric Risk of Mortality

Score III (PRISM III) at 12 h, arterial blood gases, mechanical ventilation (MV) parameters, adjunct therapies, fluid balance, and hospital outcomes. These MV data were recorded for 7 days after they met the PARDS definition. Routine arterial blood gases were measured at 6-8 AM, which corresponded with the MV setting. Patients were divided into two groups based on their risk factors of PARDS: Sepsis-related PARDS and nonsepsis PARDS. The sepsis-related PARDS group included patients who had sepsis as a risk factor for developing PARDS, whereas the nonsepsis PARDS group included patients who did not have sepsis at the time of onset of PARDS.

Definitions

Sepsis was defined as systemic inflammatory response syndrome in the presence of suspected or proven infection.[16]

Organ dysfunction criteria were defined by the International Pediatric Sepsis Consensus Conference 2005, which included cardiovascular, neurologic, hematologic, renal, and hepatic dysfunction.[16]

The percentage of fluid overload (%FO) at 72 h was defined as ([fluid intake-fluid output]/PICU admission weight ×100%) for 72 h after PARDS diagnosis.[17]

Acute kidney injury (AKI) was defined according to the Kidney Disease Improving Global Outcome.[18]

Statistical analysis

Statistical analysis was performed using the SPSS (22.0 Program: IBM, Armonk, NY, USA). We reported median and interquartile range (IQR) for continuous data and proportions for categorical variables. Patient demographics and clinical outcomes were compared between the two groups using Chi-square or Fisher's exact test for categorical variables and using the Student's *t*-test or MannWhitney *U* test for continuous data without normal distribution. Patients with conventional MV were considered for analysis of ventilation variables (PIP, MAP, Ppl, PEEP, V_T, and FiO_2). V_T was calculated using the subject's ideal body weight. Multivariable logistic regression was performed to measure the association between the significant univariate variables and organ dysfunction. A $P < 0.05$ was considered statistically significant.

Results

We screened 1226 patients who were admitted to the PICU and intubated for more than 24 h. There were 1094 patients who did not meet our inclusion criteria or met the exclusion criteria. The remaining 132 patients met either the Berlin or the PALICC criteria. Altogether 123 patients (93.2%) fulfilled the Berlin definition, and 125 patients (94.7%) fulfilled the PALICC definition. The severity of ARDS by using Berlin and PALICC definitions is shown in Figure 1. The median age was 29 months (IQR 8.199.6) and 71 (53.8%) were male. Thirty of the 132 patients died (22.7%). The median onset of PARDS was 2 days (IQR 14 days). The median PRISM III and PELOD scores were 7 (IQR 411) and 3 (IQR 08), respectively. The overall PICU mortality, hospital mortality, and organ dysfunction were 23 out of 132 (17.4%), 30 out of 132 (22.7%), and 60 out of 132 (45.4%) patients, respectively.

The most common etiologies of PARDS were pneumonia (73.5%), distantly followed by sepsis (19.7%), trauma (3.8%), aspiration (1.5%), and drowning (1.5%). Nine sepsis patients were diagnosed with sepsis and pulmonary infection. We classified 26 (19.7%) patients with sepsis-related PARDS and 106 (80.3%) patients with nonsepsis PARDS. Hemato-oncologic disease was the most common comorbidity in the sepsis-related PARDS group (46.2%). The sepsis-related PARDS patients had significantly higher severity scores, serum lactate, percentage of fluid overload within 72 h, metabolic acidosis, and low platelet count than nonsepsis PARDS patients [Table 1]. The initial MVs were similar in both groups. Clinical outcomes between sepsis-related PARDS and nonsepsis PARDS patients revealed that sepsis-related PARDS patients had a significantly higher incidence of AKI, developed septic shock, developed organ dysfunction, and mortality rate more than the nonsepsis PARDS patients.

Risk factors of organ dysfunction

There were 60 PARDS patients with organ dysfunction (45.4%). Patients with a higher PRISM III, PELOD score, positive fluid balance at 72 h, low platelet count, higher serum lactate, higher initial oxygen index, metabolic acidosis, and sepsis-related PARDS had increased organ dysfunction [Table 2]. Multivariate analysis adjusted for clinical variables (comorbidity, PELOD, PRISM III, %FO, initial oxygen index, initial arterial lactate, platelet count, and sepsis risk factor) confirmed that sepsis-related PARDS and percentage of fluid overload were significantly associated with organ dysfunction (odds ratio [OR] 11.414; 95% confidence interval [CI] 1.408-92.557, P = 0.023 and OR 1.169; 95%CI 1.012-1.352, P = 0.034) [Table 3].

The baseline characteristics of patients with organ dysfunction and without organ dysfunction in each PARDS group (sepsis-related PARDS and nonsepsis PARDS) are shown in Table 4. In both groups, organ dysfunction patients had a significantly higher severity score and a higher percentage of fluid overload at 72 h. In addition, organ dysfunction patients in the

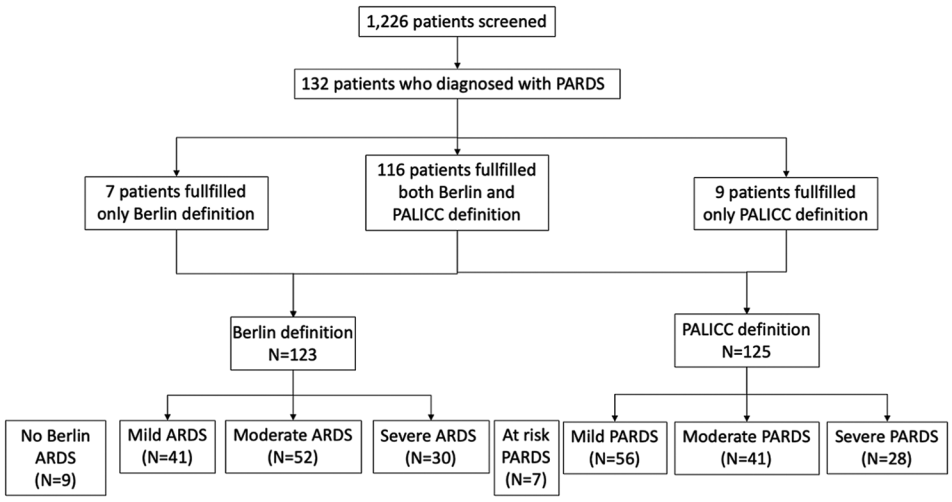

Figure 1: Flow of study in patients with pediatric acute respiratory distress syndrome by using the Berlin or the Pediatric Acute Lung Injury Consensus Conference definitions

Table 1: Baseline characteristics and outcomes

Variables	Nonsepsis PARDS (*n*=106)	Sepsis-related PARDS (*n*=26)	*P*
Age, months	28.5 (9.2-94.2)	40.8 (5.0-146.1)	0.448
Male, *n* (%)	56 (52.8)	15 (57.7)	0.827
Body surface area, m^2	0.5 (0.4-0.9)	0.6 (0.4-1.3)	0.195
Co-morbidity, *n* (%)			
Healthy	46 (43.4)	5 (19.2)	<0.001
Hemato-oncology	11 (10.4)	12 (46.2)	
Respiratory	13 (12.3)	1 (3.8)	
Cardiovascular	12 (11.3)	1 (3.8)	
Neurology	7 (6.6)	1 (3.8)	
Genetic	5 (4.7)	4 (15.4)	
Others	12 (11.3)	2 (7.7)	
PRISM III	6.0 (4.0-10.3)	10.0 (5.0-15.3)	0.004
PELOD	2.0 (0.0-7.5)	6.5 (1.0-12.3)	0.015
Fluid overload at 72 h, %	6.4 (3.5-9.9)	11.5 (5.3-14.6)	0.016
1st day of PARDS			
White blood cell count, 10^9/L	11.3 (6.7-17.3)	8.9 (3.1-15.5)	0.304
Hemoglobin, g/dL	9.9 (8.7-12.2)	10.6 (9.5-12.4)	0.293
Platelet count, 10^9/L	270 (110-399)	107 (445-191)	<0.001
Albumin, g/dL	3.0 (2.6-3.5)	3.0 (2.3-3.4)	0.298
Procalcitonin, ng/ml	1.4 (0.3-9.9)	10.9 (4.4-20.3)	0.004
PF ratio	169 (108-245)	141 (104-198)	0.185
Oxygen index	8.0 (5.1-14.6)	9.5 (6.3-13.9)	0.416
$PaCO_2$, mmHg	41.1 (36.0-51.7)	36.5 (32.8-52.3)	0.051
Bicarbonate, mEq/L	23.0 (19.4-25.9)	18.5 (17.0-24.3)	0.015
Lactate, mmol/L	1.2 (0.7-2.0)	3.0 (2.0-4.7)	<0.001
Shock, *n* (%)	34 (32.1)	23 (88.5)	<0.001
AKI, *n* (%)	14 (13.2)	8 (30.8)	0.041
Required RRT, *n* (%)	4 (3.8)	3 (11.5)	0.137
Air leak syndrome, *n* (%)	17 (16.0)	1 (3.8)	0.197
Organ dysfunction, *n* (%)	38 (35.8)	22 (84.6)	<0.001
Hospital stays, day	17.0 (9.8-32.8)	26.0 (11.5-60.0)	0.126
ICU stays, day	8.0 (5.0-13.0)	11.5 (4.0-20.0)	0.118
Nonsurviving patients, *n* (%)	19 (17.9)	11 (42.3)	0.016

PRISM III: Pediatric Risk of Mortality Score III, PELOD: Pediatric Logistic Organ dysfunction score, PF ratio: The PaO_2/FiO_2 ratio, $PaCO_2$: Partial pressure of carbon dioxide, RRT: Renal replacement therapy, ICU: Intensive care unit, AKI: Acute kidney injury, PARDS: Pediatric acute respiratory distress syndrome

nonsepsis PARDS group had a significantly higher oxygen index, lactate level, and metabolic acidosis on the first day of diagnosis than nonorgan dysfunction patients. Among patients with nonsepsis PARDS,

Table 2: Risk factors of organ dysfunction in pediatric acute respiratory distress syndrome patients

Variables	Nonorgan dysfunction (*n*=72)	Organ dysfunction (*n*=60)	*P*
Age, months	20.5 (9.3-52.1)	43.4 (6.1-134.7)	0.118
Male, *n* (%)	36 (50.0)	35 (58.3)	0.383
Body surface area, m^2	0.5 (0.4-0.6)	0.6 (0.4-1.2)	0.013
Co-morbidity, *n* (%)			
Healthy	33 (45.8)	18 (30.0)	0.001
Hemato-oncology	5 (6.9)	18 (30.0)	
Respiratory	11 (15.3)	3 (5.0)	
Cardiovascular	6 (8.3)	7 (11.7)	
Neurology	8 (11.1)	0	
Genetic	3 (4.2)	6 (10.0)	
Others	6 (8.3)	8 (13.3)	
PRISM III	5 (3-7)	10 (8-17)	<0.001
PELOD	2 (0-4)	7 (2-12)	<0.001
Fluid overload at 72 h, %	5.5 (3.2-7.7)	10.7 (6.2-14.5)	<0.001
Sepsis-related risk factor, *n* (%)	4 (5.6)	22 (36.7)	<0.001
1st day of PARDS			
White blood cell count, 10^9/L	12.0 (7.5-17.3)	10.6 (3.5-16.4)	0.259
Hemoglobin, g/dL	9.9 (8.9-11.9)	10.4 (8.7-12.5)	0.568
Platelet count, 10^9/L	294 (198-397)	123 (61-282)	<0.001
Albumin, g/dL	3.1 (2.5-3.6)	2.9 (2.5-3.5)	0.425
Procalcitonin, ng/ml	1.5 (0.2-12.5)	3.4 (0.4-31.9)	0.154
PF ratio	205 (135-262)	127 (74-191)	<0.001
Oxygen index	6.3 (4.4-11.3)	12.1 (6.4-26.6)	<0.001
$PaCO_2$, mmHg	41 (34-49)	41 (34-55)	0.591
Bicarbonate, mEq/L	23.8 (20.9-27.8)	19.9 (16.1-23.6)	0.009
Lactate, mmol/L	0.9 (0.6-1.8)	2.5 (1.7-4.9)	<0.001
Hospital stays, day	15 (9-24)	23 (10-47)	0.038
ICU stays, day	7 (5-11)	10 (5-19)	0.020
Nonsurviving patients, *n* (%)	4 (5.6)	26 (43.3)	<0.001

PRISM III: Pediatric Risk of Mortality Score III, PELOD: Pediatric Logistic Organ dysfunction score, PF ratio: The PaO_2/FiO_2 ratio, $PaCO_2$: Partial pressure of carbon dioxide, ICU: Intensive care unit

Table 3: The association between clinical variables and organ dysfunction

Variables	Multivariate OR (95%CI)	*P*
Presence of co-morbidity	1.687 (0.404-7.043)	0.473
PELOD score	1.052 (0.872-1.268)	0.597
PRISM III	1.194 (0.958-1.488)	0.115
Percentage of fluid overload	1.169 (1.012-1.352)	0.034
Sepsis risk factor	11.414 (1.408-92.557)	0.023
Lactate on 1st day of PARDS	1.902 (0.873-4.143)	0.102
Oxygen index on 1st day of PARDS	1.034 (0.972-1.099)	0.287
Platelet count	1.000 (1.000-1.000)	0.308

PELOD: Pediatric Logistic Organ dysfunction score, PRISM III: Pediatric Risk of Mortality Score III, OR: Odds ratio, CI: Confidence interval, PARDS: Pediatric acute respiratory distress syndrome

patients with organ dysfunction had significantly higher MV-related variables on day 1 (including PEEP, MAP, FiO_2) than patients without organ dysfunction. Among sepsis-related PARDS patients, MV-related parameters did not differ significantly between patients with and without organ dysfunction.

Discussion

Our prospective study reported the overall incidence of PARDS accounted for 10.7% of the screened population. The incidence of sepsis-related PARDS was 19.7%, which was comparable to other studies that reported rates ranging from 8.2% to 22%,[5,19,20] and PICU mortality rate was 30.7% (8/26) which was higher than a recent retrospective study that revealed the PICU mortality rate of sepsis-related PARDS was 24.6%.[21] A single-center retrospective study involving 203 sepsis-related PARDS from 828 sepsis patients showed that ARDS severity, PRISM III, and the number of organ dysfunction were associated with increased 90-day mortality in sepsis-related PARDS.[21] They recruited 20 patients with noninvasively ventilated PARDS, whereas our study recruited only patients with invasively ventilated PARDS. Our study found that hemato-oncologic patients, low platelet count, high severity score (PRISM III and PELOD), high serum lactate, and high procalcitonin were the risk factors for sepsis-related PARDS. Similarly, sepsis-related PARDS had higher organ dysfunction and mortality rate than nonsepsis PARDS. The phenotype of ARDS has been discussed and studied extensively over the last few decades, particularly in adults.[6,22,23] This theory is based on the fact that various biomarkers play

Table 4: Characteristics of patients who had organ dysfunction and without organ dysfunction in sepsis-related pediatric acute respiratory distress syndrome and nonsepsis pediatric acute respiratory distress syndrome

Variables	Nonsepsis PARDS (*n*=106)			Sepsis-related PARDS (*n*=26)		
	Nonorgan dysfunction (*n*=68)	Organ dysfunction (*n*=38)	*P*	Nonorgan dysfunction (*n*=4)	Organ dysfunction (*n*=22)	*P*
Age, months	20.5 (9.8-42.6)	44.8 (7.2-134.3)	0.113	74.8 (5.8-155.8)	40.8 (4.9-146.1)	0.776
Male, *n* (%)	33 (48.5)	23 (60.5)	0.311	3 (75.0)	12 (54.5)	0.614
Body surface area, m^2	0.5 (0.4-0.6)	0.7 (0.4-1.2)	0.013	0.9 (0.3-1.6)	0.6 (0.4-1.3)	0.570
Co-morbidity, *n* (%)						
Healthy	31 (45.6)	15 (39.5)	0.104	2 (50.0)	3 (13.6)	0.088
Hemato-oncology	5 (7.4)	6 (15.8)		0	12 (54.5)	
Respiratory	11 (16.2)	2 (5.3)		0	1 (4.5)	
Cardiovascular	6 (8.8)	6 (15.8)		0	1 (4.5)	
Neurology	7 (10.3)	0		1 (25.0)	0	
Genetic	2 (2.9)	3 (7.9)		1 (25.0)	3 (13.6)	
Others	6 (8.8)	6 (15.8)		0	2 (9.1)	
PRISM III	5.0 (3.0-7.0)	11.0 (5.0-20.0)	<0.001	4.5 (4.0-5.0)	10.0 (10.0-16.5)	0.006
PELOD	2.0 (0.0-4.0)	6.0 (2.0-12.0)	<0.001	0 (0-7)	7.0 (4.0-13.0)	0.054
Fluid overload at 72 h, %	5.5 (3.2-7.7)	9.3 (5.5-13.8)	<0.001	4.7 (1.7-8.2)	12.1 (6.3-15.1)	0.065
Blood culture, *n* (%)	7 (11.9)	8 (21.1)	0.258	1 (25.0)	6 (27.3)	1.000
1st day of PARDS						
White blood cell count, 10^9/L	12.2 (7.7-17.2)	10.6 (3.9-18.1)	0.422	7.5 (4.1-7.5)	9.1 (2.9-15.4)	0.867
Hemoglobin, g/dL	9.9 (8.9-11.9)	9.8 (8.7-13.2)	0.778	10.9 (9.3-10.9)	10.6 (9.5-12.2)	0.645
Platelet count, 10^9/L	305 (213-405)	132 (82-398)	0.015	159 (84-159)	103 (37-191)	0.452
Procalcitonin, ng/ml	1.5 (0.2-12.6)	1.3 (0.3-9.0)	0.862	12.1 (3.1-12.1)	20.9 (4.3-42.3)	0.752
PF ratio	206 (137-262)	119 (71-185)	<0.001	142 (114-193)	140 (87-197)	0.887
Oxygen index	6.3 (4.4-12.1)	13.3 (7.4-28.4)	<0.001	9.5 (5.9-10.9)	9.6 (6.2-18.0)	0.619
$PaCO_2$, mmHg	41 (36-50)	42 (38-56)	0.317	33 (29-37)	37 (33-54)	0.241
Bicarbonate, mEq/L	24.1 (21.4-27.9)	20.0 (14.2-23.4)	0.002	19.2 (17.2-24.1)	18.5 (16.8-24.3)	0.943
Lactate, mmol/L	0.9 (0.6-1.5)	2.3 (1.7-6.5)	<0.001	3.1 (1.8-3.1)	2.8 (1.9-4.9)	0.763
Maximum PIP	22 (18-27)	23 (20-30)	0.201	22 (19-25)	25 (19-30)	0.371
Maximum PEEP	6 (5-9)	7 (6-11)	0.019	6 (4-11)	9 (6-12)	0.268
Maximum MAP	14 (10-17)	16 (13-23)	0.010	10 (10-10)	16 (11-19)	0.338
Maximum tidal volume (ml/kg)	7 (6-8)	7 (6-8)	0.104	7 (5-8)	8 (6-8)	0.227
Maximum P_{pl}	20 (16-25)	20 (17-26)	0.392	17 (14-22)	20 (17-25)	0.254
Maximum FiO_2	0.6 (0.4-0.8)	0.8 (0.6-1.0)	0.001	0.7 (0.6-1.0)	0.7 (0.5-1.0)	0.969
Hospital stays, day	15 (9-24)	20 (10-42)	0.185	12 (9-57)	30 (13-64)	0.337
ICU stays, day	7.0 (5.0-10.7)	10 (5-19)	0.067	7 (4-46)	14 (4-20)	0.643
Nonsurviving patients, *n* (%)	4 (5.9)	15 (39.5)	<0.001	0	11 (50.0)	0.113

PELOD: Pediatric Logistic Organ dysfunction score, PRISM III: Pediatric Risk of Mortality Score III, PIP: Peak inspiratory pressure, PEEP: Positive end-expiratory pressure, MAP: Mean airway pressure, P_{pl}: Plateau pressure, PARDS: Pediatric acute respiratory distress syndrome, ICU: Intensive care unit, $PaCO_2$: Partial pressure of carbon dioxide, FiO_2: The fraction of inspired oxygen

a significant role in the development of each phenotype, resulting in distinct treatment responses and outcomes. A recent study examined biomarkers in 98 pediatric sepsis-associated ARDS patients. The result showed that indirect lung injury patients had higher endothelial activation biomarkers and worse outcomes than direct lung injury patients.[24]

The multivariate analysis showed that sepsis-related PARDS was significantly associated with organ dysfunction. As well as, the mortality rate in the sepsis-related PARDS group was twice higher than the nonsepsis PARDS group (42.3% vs. 17.9%; $P < 0.016$), which was consistent with previous studies using the PALICC definition.[5,20] The causes of deaths were most likely from organ dysfunction caused by systemic inflammation rather than isolated lung injury, as the sepsis-related PARDS group had a higher rate of organ dysfunction.

Fluid overload is a well-established risk factor for mortality, although it is unclear whether it is causal or a marker of the severity of illness. The cumulative fluid balance after day 3 of PARDS can be used to determine the characteristic of fluid balance.[25] The previous study showed fluid restriction increased ventilator-free days and decreased length of ICU stay in children with sepsis and PARDS.[26] Our study showed the percentage of fluid overload at 72 h of PARDS was significantly associated with increased organ dysfunction and mortality.

A recent literature review showed that nonpulmonary sepsis, immunocompromised host, the severity of hypoxemia, higher ventilator setting, and fluid balance were associated with increased mortality.[27] Our study found that oxygen index, acidosis, and lactate were associated with high organ dysfunction in the nonsepsis group, indicating a higher systemic severity had higher organ dysfunction in isolated pulmonary PARDS. A recent study found the worse ventilator parameter, and oxygen index, including PF ratio, was associated with higher mortality in the direct risk factor group, while lactate and pSOFA scores were associated with higher mortality in the indirect risk factor group.[19]

Our study has several strengths. This is the first large prospective, multicenter study to conduct subgroup analysis using the sepsis phenomenon. Recent research has concentrated on direct and indirect PARDS, which encompass both infectious and noninfectious spectrums within each subtype.[20] Subclassification of PARDS into distinct pathophysiologic subtypes may facilitate the development of more precise biomarker assays in future.

Limitations

There were some limitations in our study. First, there was some overlap between nonpulmonary sepsis-PARDS and pulmonary sepsis-PARDS. Clinical sepsis and pneumonia occurred in some patients concurrently at the time of the onset of PARDS. However, there were only nine patients who had pneumonia and sepsis at the time of onset of PARDS, that were classified into the sepsis-related PARDS group. The PARDS subtype was determined by a single author in each center. However, we strictly used the definition of sepsis following the international pediatric sepsis consensus conference. Second, the different centers managed PARDS differently, which may influence the outcomes. Our recruited centers were all tertiary centers with similar intensive monitoring equipment and certified ICU staff. Third, we did not include at risk for PARDS in our study since noninvasive ventilation patients were treated outside the PICU. Last, we did not evaluate prognostic biomarkers in sepsis ARDS. This knowledge gap may be further investigated in future research.

Conclusions

Sepsis-related PARDS patients had more severe illness and higher morbidities and mortality than nonsepsis PARDS patients. The percentage of fluid overload and sepsis-related PARDS were the independent risk factor of organ dysfunction in PARDS patients. In contrast to sepsis-related PARDS patients, higher respiratory indices, severity score, lactate levels, positive fluid balance, and metabolic acidosis were associated with increased organ dysfunction in nonsepsis PARDS patients.

Acknowledgments

The authors would like to acknowledge the Department of Pediatrics, Ramathibodi Hospital, Mahidol University that allowed us to analyze this project. We would like to thank Mr. Stephen Pinder, a native-speaking medical English specialist for conducting a comprehensive English language review. Furthermore, our special thanks to all participants who were recruited into this study.

Author contributions

PP and SW contributed to the design of the study, data collection, data analysis and manuscript drafting. KR, RS, and JV contributed to data collection. NA contributed to the design of the study, data collection, data analysis, and critically revised it for important intellectual content. All authors gave final approval of the version to be published.

Conflicts of interest

None declared.

Ethics approval

We obtained ethical approval from the Ethical Approval from the institutional review board. The IRB numbers were COA. MURA2017/14 (Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University) date of approval January 18, 2017, REC 60-077-19-1 (Investigational Review Board and Ethic Committee of the Faculty of Medicine, Prince of Songkla University) date of approval 15 March 2017, EMID: 0e1a497022346ec5 (Research and journal Management Committee Nakornping Hospital) date of approval November 7, 2017, IRB 1642/2559 (Med Chula IRB) date of approval December 5, 2016.

Consent to participate

Written informed consents obtained from the legal guardians of the children.

Funding

None declared.

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